In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

(Filed: December 20, 2019)

LEONORA BANTUGAN, as Representative of the Estate of MANUEL BOLOTAOLO, Deceased,	*	PUBLISHED
Petitioner,	*	No. 15-721V
v.	*	Special Master Nora Beth Dorsey
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Denial of Entitlement; Influenza ("flu") Vaccine; Lymphocytic Myocarditis; Death.
Respondent.	*	

Richard Gage, Richard Gage, P.C., Cheyenne, WY, for petitioner.
Colleen Clemons Hartley, United States Department of Justice, Washington, DC, for respondent.

DECISION[1]

I. Introduction

On July 13, 2015, Leonora Bantugan as Representative of the Estate of Manuel Bolotaolo, Deceased, ("petitioner"), filed a petition under the National Vaccine Injury Compensation Program ("Vaccine Act" or "the Program"),[2] 42 U.S.C. § 300aa-10 et seq. (2012). Petitioner alleges that Mr. Bolotaolo received a Fluzone influenza vaccination on September 18, 2014, which caused him to suffer acute fulminant lymphocytic myocarditis and death on September 21, 2014. Petition at 1-2 (ECF No. 1).

[1] Because this Decision contains a reasoned explanation for the action in this case, the undersigned is required to post it on the United States Court of Federal Claims' website in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). **This means the Decision will be available to anyone with access to the Internet.** In accordance with Vaccine Rule 18(b), petitioner has 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, the undersigned agrees that the identified material fits within this definition, the undersigned will redact such material from public access.

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to -34 (2012). All citations in this decision to individual sections of the Vaccine Act are to 42 U.S.C. § 300aa.

As her theory of causation, petitioner asserts that the influenza vaccine triggered an inflammatory process involving cytokines, leading to immune dysregulation which caused Mr. Bolotaolo's myocarditis and death. Petitioner's Post-Hearing Brief ("Pet. Posthr'g Br.") dated August 8, 2019, at 4-5 (ECF No. 87). Respondent argued against awarding compensation, stating that petitioner failed to provide preponderant evidence that Mr. Bolotaolo's myocarditis and death were caused by the influenza vaccine. An entitlement hearing was held on April 25 and 26, 2018, in Washington, D.C. The petitioner, Leonora Bantugan, her expert Dr. Alan S. Levin, and respondent's experts, Dr. Lindsay Whitton, Dr. Brent T. Harris, and Dr. Shane J. LaRue testified. After the hearing, the parties submitted additional expert reports, medical literature, and post-hearing briefs.

Petitioner, Leonora Bantugan, has faced great personal tragedy in the loss of her father, and I extend my deepest sympathy to her and her family. However, after carefully analyzing and weighing all of the evidence and testimony presented in this case in accordance with the applicable legal standards, I find that she has not met her legal burden and is thus not entitled to compensation. Specifically, petitioner failed to provide preponderant evidence that the influenza vaccination that Mr. Bolotaolo received on September 18, 2014, caused his lymphocytic myocarditis and death on September 21, 2014. Therefore, this case must be dismissed.

II. Applicable Statutory Scheme

The Vaccine Act was established to compensate vaccine-related injuries and deaths. § 300aa-10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" Rooks v. Sec'y of Health & Human Servs., 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

Petitioner's burden of proof is by a preponderance of the evidence. § 300aa-13(a)(1). The preponderance standard requires a petitioner to demonstrate that it is more likely than not that the vaccine at issue caused the injury. Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, petitioners must prove that that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface v. Sec'y of Health & Human Servs., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); Pafford v. Sec'y of Health & Human Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner who satisfies this burden is entitled to compensation unless respondent can prove, by a preponderance of the evidence, that the vaccinee's injury is "due to factors unrelated to the administration of the vaccine." § 300aa-13(a)(1)(B).

III. Procedural History

The petition was filed on July 13, 2015, accompanied by petitioner's affidavit. Medical records and a statement of completion were filed shortly thereafter. Petitioner's Exhibits ("Pet. Exs.") 1-7 (ECF No. 5). In February and March 2016, petitioner filed an initial expert report by Dr. Levin, as well as his CV and several medical articles. Pet. Exs. 8-12 (ECF Nos. 15-17). Subsequently, on July 28, 2016, respondent filed his Rule 4(c) Report, stating that the case was not

appropriate for compensation, and the expert reports of Dr. Whitton, Dr. Harris, and Dr. LaRue, along with their respective CVs and accompanying medical literature. Respondent's Report ("Resp. Rept.") (ECF No. 24); Respondent's Exhibits ("Resp. Exs.") A-B, D-E, G-H (ECF No. 26). Petitioner's responsive expert report by Dr. Levin was filed on April 12, 2017. Pet. Ex. 14 (ECF No. 34). The case was set for hearing on April 25 and 26, 2018.

The case was reassigned to my docket on March 26, 2018. Joint pre-hearing submissions were submitted on March 28, 2018. Joint Prehr'g Submissions dated Mar. 28, 2018 (ECF No. 40). On April 25 and 26, 2018, an entitlement hearing was held. During the hearing, the petitioner and her expert, Dr. Levin testified, as did respondent's experts, Dr. Whitton, Dr. Harris, and Dr. LaRue. At the conclusion of the hearing, the parties agreed to investigate whether there was tissue from the autopsy available and appropriate for PCR testing.[3] The parties were also ordered to file several documents and medical articles. Order dated April 26, 2018 (ECF No. 45).

On June 28, 2018, a telephonic status conference was held to discuss the issue of PCR testing. Order dated July 2, 2018 (ECF No. 60). Petitioner's counsel noted that while Los Robles Hospital had retained tissue blocks from the autopsy, they were fixed rather than frozen. Portions of the hearing transcript were reviewed, including testimony by Dr. Harris, respondent's expert, stating that PCR testing would be possible if the tissue had been frozen. Dr. Harris also testified that although immunohistochemical testing may be possible on fixed tissue, it was unlikely to produce meaningful results. Petitioner's counsel asked his expert, Dr. Levin, whether immunohistochemical testing would be worthwhile, and on August 1, 2018, petitioner filed a status report stating that Dr. Levin did not believe that immunohistochemical testing was necessary. Status Rept. dated Aug. 1, 2018 (ECF No. 61). Therefore, no additional testing was pursued.

From August 2018, through February 2019, the parties filed several post-hearing expert reports, documents, and medical articles. A post-hearing memorandum was filed by petitioner on April 22, 2019, by respondent on July 19, 2019, and petitioner filed her reply brief on August 8, 2019. Pet. Posthr'g Br., filed Apr. 22, 2019 (ECF No. 79); Resp. Posthr'g Br., filed July 19, 2019 (ECF No. 85); Pet. Posthr'g Reply, filed Aug. 8, 2019 (ECF No. 87). The matter is now ripe for adjudication.

IV. Issue

The issue presented is whether petitioner has proven by preponderant evidence that the influenza vaccination administered to Mr. Bolotaolo on September 18, 2014, caused his lymphocytic myocarditis and death on September 21, 2014.

V. Factual History

a. Stipulated Facts

The parties stipulated to the following facts:

[3] PCR or polymerase chain reaction testing employs a process of "amplifying low levels of specific DNA sequences . . . to levels that can be quantified by further analysis." Mosby's Manual of Diagnostic and Laboratory Tests 4 (6th ed. 2017). The test is used to identify the etiology of an infectious illness. Id.

1. Mr. Bolotaolo received a Fluzone Hd Pf 14-15 vaccination at Target Pharmacy in Simi Valley, California on September 18, 2014. Pet. Ex. 3 at 1.
2. Mr. Bolotaolo died on September 21, 2014 at Los Robles Hospital and Medical Center. Pet. Ex. 6 at 1; Pet. Ex. 7 at 1.
3. Consistent with the autopsy report, Mr. Bolotaolo's cause of death was lymphocytic myocarditis. Pet. Ex. 6 at 15.

Joint Prehr'g Submissions dated Mar. 28, 2018, at 1 (ECF No. 40).

b. Summary of Medical Records

In addition to the above stipulated facts, the following facts are relevant to my decision. Generally, the facts are not disputed by the parties.

Mr. Bolotaolo was born on November 28, 1945. Petition at 1. He was 68 years old when he received the Fluzone Hd[4] vaccine on September 18, 2014. Pet. Ex. 3 at 1; Tr. 281. His past medical history was significant for hypertensive heart disease. Pet. Ex. 1 at 4, 22-23. In 2010 and 2012, Mr. Bolotaolo had echocardiograms that revealed left ventricular dysfunction consistent with age, and mild mitral and tricuspid valve regurgitation. Id. at 4, 11, 15-17.

On September 5, 2014, Mr. Bolotaolo presented to his primary care physician, Dr. Riffal Muzaffer, for a follow-up appointment regarding hypertension and medication. Pet. Ex. 2 at 13. Physical examination and vital signs were normal. Id. at 14. Mr. Bolotaolo received the flu vaccine at issue herein on September 18, 2014 at Target Pharmacy. Pet. Ex. 3 at 1.

On September 21, 2014, Mr. Bolotaolo was brought in by his family to Simi Valley Hospital Emergency Department ("Simi Valley ED") at 1:24 PM with complaints of "not feeling well for the past 2 days with [] worsening shortness of breath on exertion, chills, body aches and generalized weakness with profuse watery diarrhea since receiving a flu shot 3 days ago." Pet. Ex. 4 at 8. Fever, weakness, and fatigue were also reported. Id. At the time of his initial physical examination, Mr. Bolotaolo was alert, cooperative, "in no acute distress," and had no neurological deficits. Id. at 9. Lung sounds were clear, and heart rate was regular, although pulse was elevated at 106. Id. Blood pressure was low at 66/30 mmHg. Id.

Diagnostic testing was ordered, and results showed that Mr. Bolotaolo had an abnormally elevated white blood count at 15.3 k/mm3, with elevated neutrophils and decreased lymphocytes. Pet. Ex. 4 at 10. Influenza A and B antigen screens obtained by nasal swab were negative. Id. at 11. Biomarkers of cardiac injury, troponin and creatine kinase ("CK"), were elevated. Id. Troponin was critically elevated at 102 and CK was very high at 2,332. Id. An EKG was abnormal, showing ST segment elevation. Id.

[4] Fluzone Hd is a high-dose vaccine indicated for active immunization against influenza virus subtypes A and B. Pet. Ex. 21 at 1. It is approved for use in persons sixty-five years of age or older. Id.

While in the Simi Valley ED Mr. Bolotaolo's condition deteriorated and he was intubated and mechanically ventilated. Pet. Ex. 4 at 11. He was transferred to Los Robles Hospital and Medical Center ("Los Robles") for emergent cardiac catheterization. Pet. Ex. 5 at 12. He was diagnosed with cardiogenic shock and had cardiac arrest. Id. Resuscitative efforts were not successful and he died at 6:08 PM. Pet. Ex. 7 at 1.

c. Autopsy

An autopsy was performed at Los Robles by Dr. Devki Patel on September 23, 2014. Microscopic examination of heart tissue revealed "diffuse infiltration by predominantly lymphocytes (T-cells [])."[5] Pet. Ex. 6 at 11. Immunohistochemical staining showed that a majority of the lymphocytes were CD3 positive.[6] Id. at 14. Lymphocytes were found between "myocytes, within interstitial fibrous tissue, and on the pericardial surface." Id. at 11. Patchy areas of the heart muscle had changes consistent with "early myocardial necrosis" or cell death. Id. "Granulomas, giant cells, eosinophils, and neutrophils [were] not identified." Id. at 12. Fungus, parasites, and bacteria were not identified. Id. "No viral inclusions" were seen. Id.

Dr. Patel noted the following:

> The cause of death is lymphocytic myocarditis leading to extensive early myocardial necrosis and eventual cardiac failure. An arrhythmia cannot be entirely excluded as the immediate cause of death . . . . Lymphocytic myocarditis can have various etiologies including viral (such [as] Coxsackie B virus, enterovirus, echovirus, adenovirus, influenza, cytomegalovirus, HHV6, and parvovirus B19), idiopathic, Rickettsial, spirochetal, autoimmune or collagen vascular disease, or drug/toxin induced. Sections of the heart show no evidence of viral inclusions or organisms. There is no evidence of autoimmune disease, vasculitis, or collagen vascular disease.

Pet. Ex. 6 at 15.

Cause of death documented on the death certificate was cardiopulmonary arrest and cardiogenic shock due to "acute fulminant lymphocytic myocarditis." Pet. Ex. 7 at 1.

d. Leonora Bantugan

Leonora Bantugan is the petitioner and the daughter of Mr. Bolotaolo. She is a registered nurse. Tr. 267. She testified that her parents moved from the Philippines to the United States in 2005, and after arriving in this country, her father received annual seasonal flu vaccinations. Id.

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[5] T lymphocytes (T cells) are a fundamental component of the adaptive immune response. Specifically, they are thymus-derived lymphocytes that confer "cell-mediated immunity" and cooperate with B lymphocytes, enabling them to synthesize antibody specific antigens. Illustrated Dictionary of Immunology 686 (3d ed. 2009) [hereinafter Immunology]; see also Janeway's Immunobiology 11-12 (9th ed. 2016).

[6] CD3 molecules are "[c]ell-surface molecules found on immune system cells" that play a role in transmitting signals to the cell interior in cell-mediated immunity. Immunology at 138-39, 788.

After her father died, Ms. Bantugan asked several physicians whether the flu vaccine could have played a role in his death, and "they all said the same thing, that [] it has not been reported." Tr. 268. Ms. Bantugan did not remember the names of any of these physicians. Tr. 271. However, she specifically recalls speaking to the physician who did the cardiac catheterization, and it was his opinion that the flu vaccine did not play a role in her father's death. Tr. 268, 271.

VI. Myocarditis

Myocarditis is an inflammatory process that affects the muscular tissue of the heart, or myocardium. Pet. Ex. 24 at 1.[7] "Viral infections are the most common cause." Resp. Ex. C, Tab 7 at 1.[8] The disease has a "wide range of clinical presentations, from asymptomatic to life-threatening" and is a recognized cause of sudden death. Pet. Ex. 24 at 2. The clinical course of myocarditis may present as acute coronary syndrome, like that associated with coronary artery disease, with EKG abnormalities such as ST segment changes, and as an acute life-threatening condition with cardiogenic shock and sudden death. Pet. Ex. 24 at 2-3; Resp. Ex. C, Tab 2 at 1.[9]

Laboratory studies may show an elevated white blood cell count and an elevated erythrocyte sedimentation rate. Cardiac biomarkers such as creatine kinase (CK) and troponin may be elevated. Resp. Ex. C, Tab 7 at 5. Diagnostic tests such as cardiac catheterization may be required to rule out cardiac ischemia. Id. Fulminant myocarditis is unusual and is characterized by "a rapidly progressive course resulting in severe heart failure and cardiogenic shock." Id. at 1.

At autopsy, myocarditis is "characterized by an inflammatory cellular infiltrate with evidence of myocyte necrosis" or cell death. Resp. Ex. C, Tab 2 at 1; Resp. Ex. I, Tab 2 at 1.[10] Myocarditis is classified based on histology into the following types: acute lymphocytic, chronic lymphocytic, giant cell, sarcoidosis, and eosinophilic. Pet. Ex. 24 at 3-4. "Acute lymphocytic myocarditis is . . . a predominant myocardial patchy infiltration of T lymphocytes, typically identified . . . by CD3 expression, with minimal fibrosis . . . . This is the most common pathologic type of myocarditis and is most frequently of viral etiology, mainly Coxsackievirus B and adenoviruses." Id. at 4. Other viral causes include enterovirus, influenza, cytomegalovirus (CMV), human herpes virus, and parvovirus. Id. at 23.

Eosinophilic myocarditis is defined as "the presence of eosinophils in significant proportions in myocardial infiltrates." Pet. Ex. 24 at 4-5. The smallpox vaccine "has been linked to

[7] William Bracamonte-Baran & Daniela Cihakova, Cardiac Autoimmunity: Myocarditis, 1003 Adv. Exp. Med. Biol. 187 (2017).

[8] Fredric Ginsberg & Joseph Parrillo, Fulminant Myocarditis, 29 Crit. Care Clin. 465 (2013).

[9] Jared Magnani & William Dec, Myocarditis: Current Trends in Diagnosis and Treatment, 113 Circulation 876 (2006).

[10] Thomas Aretz, Myocarditis: The Dallas Criteria, 18 Human Pathol. 619 (1987).

eosinophilic myocarditis." Resp. Ex. A at 3. Eosinophilic myocarditis has been reported after vaccination for several diseases including tetanus and smallpox." Resp. Ex. C, Tab 6 at 6.[11]

Using histology and clinical course, myocarditis may be classified into four groups, fulminant, acute, chronic active, and chronic persistent. Resp. Ex. I, Tab 4 at 1-2.[12] Fulminant myocarditis has a distinct onset of symptoms, and initial presentation may be characterized by cardiogenic shock and severe left ventricular dysfunction, which may lead to either complete recovery or death. Id. at 2. The clinical presentation of myocarditis has also been classified into four presentations: acute coronary syndrome-like, new onset (or worsening of heart failure), chronic heart failure, and life-threatening. Resp. Ex. I, Tab 3 at 7.[13] Acute coronary syndrome-like frequently begins one to four weeks after "a respiratory or gastrointestinal infection" and the patient may have EKG changes and increased troponin levels. Id. Chronic heart failure patients have experienced symptoms for greater than three months. Id. And life-threatening condition myocarditis patients may present with cardiogenic shock and severely impaired left ventricular function. Id.

VII. Expert Opinions

a. Petitioner's Expert, Dr. Alan S. Levin

Dr. Levin attended medical school at the University of Illinois in Chicago, then completed a one-year fellowship in pediatric immunology at Harvard University, followed by an internship at Boston Children's Hospital. Tr. 7. He subsequently completed a postdoctoral fellowship in pediatric immunology and then served in the military. Id. Upon completion of his military service, Dr. Levin did a postdoctoral fellowship at the University of California San Francisco, and then joined the faculty there as an Adjunct Instructor in Pediatrics in 1971. From 1972 to 1978, Dr. Levin was an Assistant Professor of Immunology, and from 1978 to 1988, his title was Adjunct Associate Professor of Immunology. Pet. Ex. 11 at 3. Dr. Levin was also in the private practice of medicine from 1981 until 1993. He has held admitting privileges at the University of California San Francisco Hospitals from 1971 to present. He is board certified in allergy and immunology, pathology (but not anatomic pathology), and emergency room medicine. Tr. 11, 54-55.

While in private practice, Dr. Levin cared for patients with autoimmune illnesses, AIDS, and cancer. Tr. 8. He provided health care in a large AIDS clinic, and from 1985 to 1990 performed approximately 100 autopsies on AIDS patients. Tr. 57. Myocarditis was very common in this population. Id. From the 1970's to the mid 1990's, Dr. Levin published a number of articles and book chapters, primarily on issues related to immunology. See Pet. Ex. 11 at 4-5.

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[11] Lori Blauwet & Leslie Cooper, Myocarditis, 52 Progress Cardiovascul. Diseases 274 (2010).

[12] Eric Lieberman & Noel Rose, Clinicopathologic Description of Myocarditis, 18 J. Am. Coll. Cardiol. 1617 (1991).

[13] Alida Caforio et al., Current State of Knowledge on Aetiology, Diagnosis, Management, and Therapy of Myocarditis: A Position Statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases, 34 Eur. Heart J. 2636 (2013).

Dr. Levin attended law school at Golden Gate University in San Francisco, obtaining his J.D. in 1995. Pet. Ex. 11 at 1. He was Of Counsel to the law firm of White & Meany in Reno, Nevada from 1997 to 2001. Id. at 3. From 2001 to present he has been in the private practice of law as Alan S. Levin, M.D., J.D. Id. He is admitted to practice law in California, Texas, Nevada, the United States Courts of Appeals for the Armed Forces, and the Supreme Court of the United States. Id. at 1.

Dr. Levin spends approximately 90% of his time practicing law, primarily in the area of toxic torts. Tr. 48. With regard to his medical practice, he sees one to four patients per month. Tr. 50.

1. Causation Opinion

i. Althen Prong One – Can the Influenza Vaccine Cause Lymphocytic Myocarditis

Dr. Levin opines that the Fluzone Hd vaccine that Mr. Bolotaolo received on September 18, 2014, was the cause or a substantially contributing factor to his death on September 21, 2014. [14] In his first expert report, Dr. Levin posits that the viral antigens in the flu vaccine activated "the adaptive immune system T cells in a pre-primed healthy adult" resulting in a "massive infiltration of CD3 positive T cells[,]" leading to myocarditis and death. Pet. Ex. 8 at 1, 3-4. At the hearing, however, Dr. Levin changed his opinion, and testified that the innate immune system[15] was the primary player. He opined that cytokines were released in response to the flu vaccine through a process called "pattern recognition." Tr. 275-76. He testified that then other immune cells (T cells and B cells) were recruited, and these secreted antibodies, as part of the adaptive immune system.[16] Id. Dr. Levin testified that while both immune systems were implicated, the myocardial damage was done primarily by the innate immune system. Tr. 276.

According to Dr. Levin, there was "an inflammatory response associated with these T cells which in turn are activated by cytokines." Tr. 23. Cytokines are "basically hormones that are secreted by cells called macrophages." Id. Macrophages "ingest antigens, or [] in the case of vaccines, carbohydrates from the virus. And it makes the body think that it's infected by that virus and causes the body to try and protect itself." Id. "[I]n this particular situation . . . the regulatory mechanism that control[s] these immune responses fail[ed]" and as a result there was immune

[14] The date of death in Dr. Levin's expert report, September 24, 2014, is incorrect. The date was September 21, 2014. Pet. Ex. 8 at 1.

[15] The innate immune system is the "natural or native immunity present from birth[,] [] designed to protect [] from injury or infection without previous contact with infectious agents[,] [a]ttributable to physical, chemical, and molecular defenses that prevent contact with antigens in a nonspecific manner." Immunology at 391. Phagocytes and cytokines are important players in natural innate immunity. Id.

[16] Adaptive immunity provides "[p]rotection from an infectious agent as a consequence of clinical or subclinical infection with that agent or by [] immunization against . . . it." Immunology at 18. Adaptive immunity is "mediated by B and T lymphocytes following exposure to a specific antigen." Id.

dysregulation which led to tissue destruction. Tr. 24. Dr. Levin opined that the vaccine is injected intramuscularly, and the antigens in the vaccine are picked up and presented onto the surface of dendritic cells, and then transferred to T lymphocytes, which attach to monocytes and T cell receptors. This "two-fold stimulation" causes the immune cells to begin secreting inflammatory cytokines. Tr. 84. The immune cells multiply to increase protection. In the rare case, Dr. Levin asserts that this immune process becomes dysregulated and the proliferation of immune cells does not stop, and instead causes a "disastrous inflammatory response." Id.

Dr. Levin testified that the immune response here involved T cells, which is different than the immune response involving B cells seen in hypersensitivity myocarditis. Tr. 89. Hypersensitivity myocarditis is characterized by eosinophils and not T cells (lymphocytes). Id. Myocarditis caused by a drug or toxin sensitivity would be characterized by B cells and eosinophils, not T cells, as seen in the autopsy in this case. Id.

Dr. Levin opined that the body's immune response to the influenza virus and the influenza vaccine are similar. Tr. 42, 62-63. He asserts that for the influenza vaccine to be effective, it must "evoke an immune response" and trigger the proinflammatory cytokine response so that when a person is exposed to the virus, the reactive immune cells elicited due to vaccination will prevent disease. Tr. 42. Dr. Levin opines that some of the antigens in the influenza vaccine are the same as those in the influenza virus. Tr. 62-63. While changes are made to the influenza virus to "keep the virus from replicating," Dr. Levin opined that the "antigenicity of the virus" is retained to ensure that the vaccine will activate the immune system. Tr. 278. He testified that "the immune activation of the vaccine is as intense, if not more so, that the natural exposure" to the virus. Id. He asserts that myocarditis is induced by viral antigens resulting in an infiltration of T lymphocytes into heart muscle and that the presence of the CD3+ T cells indicates a "severe reaction against a viral antigen." Pet. Ex. 8 at 1, 3.

The premise of Dr. Levin's theory is that since the influenza infection can cause lymphocytic myocarditis, so can the influenza vaccine. See Tr. 41-42. Acute lymphocytic myocarditis is a "well-known complication of influenza infection." Pet. Ex. 8 at 3; see also Tr. 43. Specifically, Dr. Levin opines that it is the body's immune response to the virus, and not the virus itself, which causes lymphocytic myocarditis. Tr. 43. It is the "body's response to invasion" by a virus that "causes the release of . . . proinflammatory cytokines, and the inflammatory process is what causes the disease." Tr. 44.

Dr. Levin cites the Ukimura article in support of his opinion that myocarditis is a well-known complication of influenza infection. Tr. 43. In Ukimura, the authors state that acute myocarditis is a well-known complication of influenza infection but that "fulminant myocarditis resulting from influenza A viral infection is rare." Pet. Ex 10 at 1.[17] The authors examine the incidence of myocarditis associated with the flu pandemic of 2009 by reviewing medical literature, identifying 58 reported cases of myocarditis associated with the influenza viral infection. Dr. Levin concedes, however, that Ukimura studied influenza viral infection, and not the influenza vaccine. Tr. 65-66.

[17] Akira Ukimura et al., Myocarditis Associated with Influenza A H1N1pdm2009, Influenza Res. Treatment, Nov. 2012, at 1-8.

Moreover, Ukimura does not support Dr. Levin's assertion that it is the immune response to the virus, and not direct effect of the virus that causes injury. While the authors do discuss proinflammatory cytokines, this is in context with "the direct effect of [the] influenza virus infection" and its role in the pathogenesis of myocarditis. Pet. Ex. 10 at 4.

Dr. Levin also testified that the terms "infection" and "vaccine reaction" were synonymous. Tr. 88-89. At the hearing, Dr. Levin agreed to provide medical literature in support of his opinion that the immune response to viral infection is the same as the immune response to vaccines. Tr. 299. Dr. Levin submitted several articles,[18] however, they do not appear to be on point with the question asked, or with the facts and circumstances present here.

Dr. Levin also cited several articles in support of his opinions. In the Amoah article, the authors discuss the "complex interactions between cardiac fibroblast cells and immune cells" that contribute to myocarditis. Pet. Ex. 22 at 7.[19] Several of the mechanisms proposed by Dr. Levin are covered in the article, including "pattern recognition" and the role of dendritic cells in both innate and adaptive immune responses. The authors state that "[v]arious innate and adaptive immune cells have been reported to be involved in the pathogenesis of myocarditis including inflammatory monocytes, neutrophils, macrophages and CD4+ Th cells." Pet. Ex. 22 at 3. However, in this case, monocytes, neutrophils, and CD4+ cells were not reported at autopsy. Amoah does reference T cell lymphocytic proliferation in association with autoimmune myocarditis, but these cells were found along with "macrophage antigens from giant cells." Id. at 5. Giant cells were not seen in the autopsy here. See Pet. Ex. 6 at 12. And in Song (Pet. Ex. 23),[20] the authors studied dysregulation of CD4+ cells as they related to autoimmune myocarditis. However, CD4+ cells were not reported as found in Mr. Bolotaolo's autopsy. Since vaccines are not discussed, and the histopathology discussed in Amoah and Song is not the same as that found at autopsy in this case, it is not clear how these articles support Dr. Levin's mechanistic theory.[21]

Another article filed by petitioner after the hearing is entitled, "The Overview on Cardiac Autoimmunity and Myocarditis" by Bracamonte-Baran and Cihakova. The article states in pertinent part:

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[18] Dr. Levin offered three exhibits that appear to be in response to this request. See Ronald Glaser et al., Stress-Related Changes in Proinflammatory Cytokine Production in Wounds, 56 Arch. Gen. Psychiatry 450 (1999); I. Steiner et al., Transient Immunosuppression: A Bridge Between Infection and the Atypical Autoimmunity of Guillain-Barré Syndrome?, 162 Clin. Experimental Immunol. 32 (2010). These articles are filed as Exhibits 25-26. Exhibit 27 is an illustration entitled Acute Infectious Colitis.

[19] Prince Amoah et al., Immunopathogenesis of Myocarditis: The Interplay Between Cardiac Fibroblast Cells, Dendritic Cells, Macrophages and CD4+ Cells, 82 Scand. J. Immunol. 1 (2015).

[20] Howard Song et al., Specialized CC-Chemokine Secretion by Th1 Cells in Destructive Autoimmune Myocarditis, 21 J. Autoimm. 295 (2003).

[21] Moreover, Dr. Levin's discussion was vague and he did not explain the distinction and/or relationship between the CD3+ cells found in Mr. Bolotaolo's autopsy, and the CD4+ cells described in Amoah and Song.

> Acute Lymphocytic myocarditis is characterized by a predominant myocardial patchy infiltration of T lymphocytes, typically identified in immunohistochemistry [] by CD3 expression, with minimal fibrosis. As expected, areas of lymphocyte infiltration co-localize with CD68+ macrophages.[22] This is the most common pathologic type of myocarditis and is most frequently of viral etiology, mainly Coxsackievirus B and adenoviruses.
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> Pet. Ex. 24 at 4.

Thus, lymphocytic myocarditis is thought to be caused by viral infection. The article does not state or suggest that viral infections and vaccines trigger an identical immune response.

Dr. Levin also cited an article by Feeley et al. In Feeley, published in 1999, researchers reviewed myocardial tissue from 163 autopsies to study the incidence of myocarditis and investigate the number of T lymphocytes seen in normal and abnormal myocardium. Pet. Ex. 9 at 1.[23] The authors state that "[r]ecent advances in immunohistochemistry have led to the understanding that a variety of cells, including macrophages, T, B and NK (natural killer) lymphocytes, all play a role in the acute phase of myocyte damage." Id. at 2. They describe a potential mechanism for chronic myocarditis, which while "still largely unclear," may "represent a form of autoimmune cytotoxic T cell response." Id. Dr. Levin confirmed that his theory here is the "autoimmune cytotoxic T cell response" described in the Feeley article. Tr. 81.

In addition to medical literature, petitioner also filed an exhibit identifying two VAERS[24] reports of cases of myocarditis associated with the influenza vaccine. See Pet. Ex. 12. In the first report, VAERS ID: 249021-1, the influenza vaccine was administered November 3, 2005, and the child died November 10, 2005. Publicly available data reveals that the child, age one, also received haemophilus B conjugate and pneumococcal vaccines on the same date. Court Ex. 1 at 1. The adverse event description states that the infant was admitted in heart failure and died on November 10, 2005. Id. at 2. The child had been "[i]ncreasingly cranky for 2 days proceeding admission to hospital." Id. The child had a current illness, described as a history of RAD (reactive airway disease), was a premie (premature), and had a history of asthma. Id. Medications the child was taking at the time of vaccination included, "Pulmicort, Zantac, Singulair, Albuterol, [and] AccuNeb." Id. No autopsy findings or myocardial histology information was included in the report.

The second report, VAERS ID: 393060-1, reported on a patient, age forty-two, who received the H1N1 monovalent influenza vaccine on November 17, 2009. Court Ex. 1 at 3. The patient received the vaccine two and one-half months prior to his death on February 9, 2010. Id.

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[22] CD68+ macrophages were also seen at autopsy here. Pet. Ex. 6 at 14.

[23] K.M. Feeley et al., Necropsy Diagnosis of Myocarditis: A Retrospective Study Using CD45RO Immunohistochemistry, 53 J. Clin. Pathol. 147 (2000).

[24] VAERS is the Vaccine Adverse Event Reporting System. The two events reported in Pet. Ex. 12 can be retrieved at https://vaers.hhs.gov/data.html. They have also been filed as Court Exhibit 1.

The description stated: "[u]nsure if related." Id. An "[a]utopsy revealed Giant cell myocarditis." Id. The history was significant for "sleep apnea, migraines, obesity, insomnia" and tobacco use. Id. at 4. Medications at time of vaccination included Trazodone, Topamax, Prilosec, and Klonopin, among others. Id.

Dr. Levin did not testify about these reports at the hearing.

ii. Althen Prong Two – Did the Influenza Vaccine Cause Mr. Bolotaolo's Lymphocytic Myocarditis and Death

Dr. Levin testified that Mr. Bolotaolo's clinical course following vaccination, including his presentation to the emergency room on September 21, 2014, and subsequent death was consistent with the findings on autopsy and diagnosis of diffuse lymphocytic myocarditis, with CD3 expression and T cell involvement in the ventricles, and extensive early necrosis of heart muscle. Tr. 14, 20. Mr. Bolotaolo's complaints of "worsening shortness of breath on exertion, chills, body aches, and generalized weakness with profuse watery diarrhea" three days after the flu shot were "side effects of the cytokines being released [] through vaccination."[25] Tr. 14-15. Dr. Levin opined that the presence of diffuse T cells was evidence of the inflammatory process caused by cytokines, activated by antigens. Tr. 27. He emphasized that these antigens could be triggered by a "live infected virus or a vaccine." Id.

Dr. Levin testified that Fluzone Hd is a higher potency vaccine with a larger dose of antigen, making its effect more robust. Tr. 12. The high dose vaccine is given to older persons who have "weaker immune systems and therefore [] need a larger dose of antigen to respond appropriately." Tr. 13. In support of this opinion, petitioner filed information about the side effects of high dose Fluzone (Fluzone Hd), which include drowsiness, lethargy, cough, diarrhea, and tachycardia. Pet. Ex. 14 at 2-4.[26] The literature does not identify myocarditis as an adverse reaction, but one article does reference pericarditis.[27] See id. Dr. Levin testified that the mechanism of inflammation is the same for myocarditis as it is for pericarditis. Tr. 38-41.

While the autopsy here showed "a massive infiltration of CD3 positive T cells" there were no "viral inclusions or organisms" found, which Dr. Levin believes indicates that "the heart was not infected with [a] viable virus." Pet. Ex. 8 at 4. Dr. Levin testified that the "the complete absence of

[25] Dr. Levin testified that these side effects are warned about in the vaccine package insert. See Pet. Ex. 14 at 2-4.

[26] The information filed as Exhibit 14 relates to Fluzone Hd, 2016-2017 formula, not the formula for the vaccine given to Mr. Bolotaolo in 2014. The correct package insert was filed as Pet. Ex. 21, and it does not identify pericarditis or myocarditis as a reported event. See Pet. Ex. 21 at 1-19.

[27] Petitioner's Exhibit 14 appears to be from an internet website, www.drugs.come, and the reference related to pericarditis is difficult to discern.

any viral inclusions or organisms . . . indicates that the heart was not infected with [a] viable virus" and this "directly implicates the viral antigens in the vaccine."[28] Id.

The fact that there was no alternative cause found for Mr. Bolotaolo's myocarditis was an important factor contributing to Dr. Levin's opinion. He testified that the autopsy did not show evidence of any viral infection, or fungal, parasitic, or bacterial infection, and there was no evidence of viral inclusion bodies.[29] Thus, Dr. Levin opined that Mr. Bolotaolo's lymphocytic myocarditis was not caused by viral, fungal or bacterial infection, but by vaccination. Tr. 26-28.

Another important fact to Dr. Levin was the lack of evidence of an inflammatory process anywhere else in the body, other than the heart. Tr. 27, 94. If a viral infection had caused the decedent's demise, Dr. Levin would have expected to see evidence of infection in the lungs and gastrointestinal tract. Tr. 28. Dr. Levin testified that Coxsackievirus affects multiple organs, and if it was the cause, he would expect to find "an inflammatory process in the colon" but there was no such finding on autopsy.[30] Tr. 28-30.

Dr. Levin testified that Mr. Bolotaolo's increased white blood cell count was "absolute and unequivocal proof that there was an elevation" in cytokines (tumor necrosis factor alpha, IL-1, and IL-6) which would be expected after vaccination. Tr. 272-73. However, he agreed that the elevation in these cytokines is also consistent with a viral infection. Tr. 282.

According to Dr. Levin, Mr. Bolotaolo's prior history of arteriosclerosis could have contributed by making his heart weaker and a target for an inflammatory process. Tr. 75. Dr. Levin called this a "transitory susceptibility to infection," due to "genetics, [] environment[, and] age." Tr. 87. He opined that Mr. Bolotaolo's immune system was susceptible due to past vaccinations or previous viral exposure, which caused a "disastrous inflammatory response." Tr. 84.

iii. Althen Prong Three – Appropriate Temporal Association

Mr. Bolotaolo received the influenza vaccination on the morning of September 18, 2014 and died on September 21, 2014. According to the medical records documented when he presented to Simi Valley ED on September 21, 2019, he had not felt well for two days, with "worsening shortness of breath on exertion, chills, body aches and generalized weakness [] since receiving a flu shot." Pet. Ex. 4 at 8. Dr. Levin testified that Mr. Bolotaolo became symptomatic on the evening of September 18, indicating a release of cytokines. Tr. 282, 286. He further testified that myocardial damage was "likely caus[ed]" by an innate immune response, not an adaptive immune antibody response. Tr. 276. The temporal association of myocarditis and death three days post-vaccination

[28] At the hearing, Dr. Levin seemed to soften his position on this point a bit. He testified that while the absence of viral inclusions was not dispositive, he believed it was a "factor[] that point[s] towards the vaccine" as the cause. Tr. 73.

[29] Dr. Levin defined inclusion bodies as "products of either dying tissues or the virus itself" that stain in a characteristic manner. Tr. 27.

[30] Dr. Levin agreed that on autopsy the colon showed "chronic lymphocytic inflammation with eosinophils" but attributed that finding to "diverticulitis [which] caused chronic inflammation." Tr. 92.

was "perfectly reasonable." Tr. 46. "Symptomatic, disastrous myocardiopathy would take two or three days." Tr. 69.

Dr. Levin cites the vaccine package insert in which the manufacture warns that systemic adverse reactions "occur within the first three days." Pet. Ex. 29 at 2 (citing Pet. Ex. 15 at 5). He opines that because Mr. Bolotaolo had many prior exposures to the influenza virus, the timeframe between vaccination and immune response was shortened to one to three days. See Pet. Ex. 29 at 2 (citing Pet. Ex. 31 at 11).[31] Also, Dr. Levin opined that given Mr. Bolotaolo's age (68), he was exposed to the influenza virus many times before, and thus, his immune system would have reacted quickly and been primed to react to the flu antigen in the vaccine. For these reasons, he would have had a more rapid immune response, ranging between one to three days. Tr. 70-71.

In support of his opinions, Dr. Levin cites the Song study, in which severe infiltration/inflammation of heart tissue was seen at day three, with "progression of the inflammatory process leading to significant loss of myocyte mass" demonstrated at seven days. Pet. Ex. 23 at 4.

Another article cited by Dr. Levin, and authored by Bracamonte-Baran and Cihakova, published in 2017, provides current information about the timeframe between infection and onset/peak of myocarditis. Ex. 24 at 8-11. The authors also describe two animal models using Coxsackievirus B3, an enterovirus associated with human viral myocarditis. Id. at 8. One model "induces severe acute myocarditis with significant tissue damage and sudden death occurring within the first week of direct intraperitoneal infection." Id. The second model induces a milder condition that progresses to chronic myocarditis and dilated cardiomyopathy. In it, the inflammatory phase occurs 7 to 14 days after infection. Id. at 11.

b. Respondent's Expert, Dr. James Lindsay Whitton

Dr. Whitton obtained degrees in molecular biology and medicine, as well as his Ph.D. in Herpesvirus transcription, from the University of Glasgow, Scotland. Tr. 154. He did internships in medicine and surgery, but left clinical medicine to join the Department of Immunology at the Scripps Clinic in La Jolla, California as a senior research associate in 1984. Tr. 155. He has remained at Scripps since then, becoming a Professor in the Department of Immunology in 1998. Id.[32] Dr. Whitton's areas of expertise include viral pathogenesis and immune responses to viruses and vaccines. Tr. 159. He has studied the Coxsackievirus for 24 years, and has had an ongoing interest in Coxsackie viral myocarditis. Tr. 160.

[31] Adverse Effects of Vaccines: Evidence and Causality 51-52 (Kathleen Stratton et al. eds., 2011)

[32] In Petitioner's Reply Brief (ECF No. 87), counsel argues that Dr. Whitton is "100% dependent upon the Department of Health and Human Services, [r]espondent, for his salary and the funding [and research]," and this "raises the spector of bias." Petitioner asks that I consider the possibility of bias, but did not file a motion to strike or exclude Dr. Whitton's opinions or testimony, and thus, I have not formerly adjudicated the issue. I have, however, considered the issue and its implications in giving weight to the opinions and testimony of Dr. Whitton.

1. Causation Opinion

Dr. Whitton disagrees with Dr. Levin's premise that the influenza vaccine can trigger an immune response like that of the influenza virus so as to cause lymphocytic myocarditis. Tr. 166-67. Dr. Whitton did agree that the smallpox vaccine has been associated with eosinophilic myocarditis, but he opined there is "no evidence that other vaccines can trigger this disease." Resp. Ex. A at 3. Unlike the smallpox vaccine, Dr. Whitton explained that the influenza vaccine Fluzone Hd is a killed virus vaccine in which the virus is treated with a chemical that splits the virus in part.[33] Tr. 167. The vaccine contains antigens from three flu viruses, two from Influenza A and one from Influenza B, but does not contain an adjuvant. Id. The viral antigens in the vaccine do not replicate. Tr. 172. Once administered, viral antigens in the vaccine are taken up by macrophages and dendritic cells. Id.[34] T cells recognize the foreign antigens and begin to multiply, but this process take time. Id.

In contrast, Dr. Whitton testified that once infected with a live influenza virus, the virus replicates rapidly "to millions upon billions of copies of the virus . . . over a period of [] days." Tr. 168. Myocarditis caused by viral infection implicates two mechanisms. The first is "direct virus-mediated lysis or destruction of the infected heart muscle cell." Tr. 175. The second is cardiac destruction due to the immune response "which is trying [] to contain the infection." Tr. 174. Dr. Whitton agrees with Dr. Levin that the influenza virus can cause myocarditis, albeit a rare phenomenon. When it does occur, injury is caused by direct viral mediated cell lysis, and secondarily, the immune response to the virus. Tr. 201.

In support of his opinion that the influenza vaccine does not cause lymphocytic myocarditis, Dr. Whitton cited a number of articles. The article published in 2010 by Blauwet and Cooper, confirms Dr. Whitton's testimony that viral infection is "the most common cause of myocarditis." Resp. Ex. C, Tab 6 at 1. The article also corroborates Dr. Whitton's explanation of the mechanism by which viruses cause myocarditis. "Viruses that evade the innate immune system replicate, producing viral proteins that cause direct myocardial injury." Id. at 7. "Acute injury leads to myocyte damage, which in turn activates the innate and humeral immune system, leading to severe inflammation." Id. at 1. In the majority of cases, "the immune reaction is eventually down-regulated and the myocardium recovers[,]" however, in some cases, inflammation may progress to "ongoing myocyte damage" and death.[35] Id. With regard to vaccine etiology, the authors note that "[e]osinophilic myocarditis has been reported after vaccination for . . . tetanus and smallpox." Id. at 6. They do not report any case of myocarditis associated with the influenza vaccine.

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[33] For a description of the process use to create the "split virus" used here, see Pet. Ex. 21 at 9.

[34] A macrophage is a "large mononuclear phagocytic cell" active in innate immunity. It also acts as an "antigen-presenting cell in both humoral and cell-mediated immunity." Immunology at 472. Dendritic cells are also "antigen presenting cells . . . that are powerful activators of T cell responses." Id. at 220.

[35] For a comprehensive explanation of the stages of viral myocarditis see "Fulminant Myocarditis" by Ginsberg and Parrillo, filed as Resp. Ex. C, Tab 7 at 4.

The Engler et al. study, cited by Dr. Whitton, was published in 2015 and it prospectively examined the incidence of myocarditis/pericarditis associated with smallpox and influenza vaccines. Resp. Ex. C, Tab 1 at 1.[36] Of the 1081 smallpox vaccine recipients, four experienced myocarditis and one had pericarditis, an "incidence rate more than 200-times higher" than would be expected. Id. at 2. There were no cases of myocarditis/pericarditis in the 189 who received the influenza vaccine.[37] Id.

Further, in the influenza vaccine group, the cardiac-specific enzyme troponin was unchanged post-vaccination, unlike the smallpox vaccine group, which had 31 vaccinees with elevated troponin levels. The authors observed that "the fact that there were no changes in the [influenza vaccine recipients] supports that whatever the mechanism, it remains probable that the transient troponin elevations are linked to the immune activating stressors associated with the [smallpox] vaccination." Resp. Ex. C, Tab 1 at 13. The authors did not conclude that smallpox and influenza vaccines trigger a similar immune mechanism.

Generally, Dr. Whitton testified that he did not understand the petitioner's theory of causation. Tr. 182. He testified that the idea that the flu vaccine can cause myocarditis in the same manner as a viral infection is a new concept. Id. Fundamentally, Dr. Whitton disagrees with Dr. Levin that viral antigens from the flu vaccine stimulate the innate immune system. Tr. 168, 186. He explained that the primary trigger of the innate immune response in this context is nucleic acids. Id. Dr. Whitton testified that it is "the nucleic acids [RNA of the virus] that trigger the innate immune system." Tr. 168. Dr. Whitton thinks it is more likely that the decedent's myocarditis was caused by the Coxsackievirus then the flu vaccine. Tr. 176. However, because no specific virus was identified,[38] Dr. Whitton did not reach a diagnosis of Coxsackie viral myocarditis. Id.

Dr. Whitton opines that if Dr. Levin's theory is correct, the appropriate mechanism would be the adaptive immune response. Tr. 186. However, Mr. Bolotaolo received nine prior flu vaccines, and therefore, Mr. Bolotaolo "previously encountered the relevant antigens" but did not have myocarditis. Tr. 192. Dr. Whitton suggested that an adaptive immune response that occurred after numerous prior exposures weighs against a theory invoking the adaptive immune response. Tr. 192-93. In support of this opinion, Dr. Whitton cited an article by Cohen et al., in which the authors studied cytokine levels in smallpox vaccine recipients after primary vaccination and revaccination. Resp. Ex. L at 1. The authors found that primary vaccine recipients had a higher frequency and more prolonged duration of symptoms than revaccinated persons. Id. at 4. They concluded that "primary vaccine recipients are significantly more likely than revaccinated patients to have symptoms and increased levels of cytokines after vaccination." Id. at 9. Their finding is consistent with other observations that "severe adverse events . . . occurred 10 times more often in primary vaccine recipients that in revaccinated subjects." Id. at 9.

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[36] Renata Engler et al., A Prospective Study of the Incidence of Myocarditis/Pericarditis and New Onset Cardiac Symptoms Following Smallpox and Influenza Vaccination, 10 PlosOne e0118283 (2015).

[37] The authors note that the small size of the influenza vaccination group (189) limited the findings. Resp. Ex. C, Tab 1 at 13.

[38] PCR testing was not done and thus, there is no confirmation of a viral infection. See Tr. 152.

Further, Dr. Whitton asserts that there is no support for Dr. Levin's theory in the medical literature or VAERS reports. Tr. 194. Petitioner cited two VAERS reports of myocarditis associated with the flu vaccine. Dr. Whitton opines that these are not relevant to the facts and circumstances here. Id. VAERS report 249021-1 involves the death of a one-year-old seven days after receipt of Fluzone, HIB,[39] and Prevnar[40] vaccines. The child had a history of asthma and was on a number of medications to treat that condition at the time of vaccination. The histology of the myocarditis was not reported. Resp. Ex. A at 6; Pet. Ex. 12. The second report, 393060-1, involved a 42-year-old who died 84 days after receiving the flu vaccine. An autopsy revealed giant cell myocarditis. Resp. Ex. A at 7; Pet. Ex. 12.

As for the temporal association between the vaccine and myocarditis, Dr. Whitton testified that it is "not conceivable" that a vaccine could cause the number of lymphocytes seen in the heart tissue at autopsy within 24 to 48 hours after vaccination.[41] Tr. 296. He explains that two to three days after viral infection, there are "billions of viruses replicating in the heart" but no "detectable myocarditis because there aren't yet enough antigen-specific T cells in the body to cause histologically-visible myocarditis." Resp. Ex. U at 1.

Dr. Whitton described mice studies done in his lab with a strain of Coxsackievirus ("CVB3") known to cause myocarditis. Four days after the mice were infected with the virus, they appeared ill. Lymphocytic myocarditis, however, was not found on autopsy until day six to eight. Tr. 199. Dr. Whitton asserted that it takes time for myocarditis to develop, even when the mice are infected with a live virus. Tr. 178-79. Therefore, Dr. Whitton opines that in this case, the time from vaccination to myocarditis is too short and not plausible. See generally Resp. Ex. U.

In support of his opinion on temporal association, Dr. Whitton filed an article by Esfandiarei and McManus which describes the phases of viral myocarditis in experimental mice models. The acute viremic phase begins approximately three to four days after infection and "is characterized by prominent virus replication in blood and infected tissues." Resp. Ex. C, Tab 8 at 8.[42] At this point, there is also acute injury of myocardium, "in the absence of inflammatory infiltrates." Id. Cytokine release also occurs during the acute phase. Id. Next is the subacute phase, which occurs approximately 14 days after infection. Id. In this phase, the virus stimulates "a considerable increase in lymphocytic infiltration and inflammatory cytokine release within the infected heart." Id.

In the Engler article, the authors note that "[t]he peak immune inflammatory activation pattern following [smallpox] vaccine occurs between day 8-9 (with a range of day 4-27) post[vaccination] . . . . These cytokine elevations mirrored our observed timeline for peak incidence

[39] HIB is the haemophilus B conjugate vaccine (PEDVAX HIB). Court Ex. 1 at 1.

[40] Prevnar is the pneumococcal 7-valent vaccine. Court Ex. 1 at 1.

[41] The date of vaccination was September 18, 2014, and date of death was September 21, 2014, which is three days, not 24 or 48 hours.

[42] Mitra Esfandiarei & Bruce McManus, Molecular Biology and Pathogenesis of Viral Myocarditis, 3 Ann. Rev. Pathol. Mech. Disease 127 (2008).

of [troponin] elevations . . . suggesting inflammation as the mechanistic link." Resp. Ex. C, Tab 1 at 12. Elevated troponins were seen beginning day six, with a range from six to 28 days. Id. at 10.

Dr. Whitton also filed articles by Cohen et al. and Whitmire et al. to support his position that the interval between vaccination and myocarditis in this case is too short to support causation. In Cohen, cytokine levels began to increase four to five days after smallpox vaccination and peaked at eight to 11 days. Resp. Ex. L at 1.[43] In Whitmire, researchers found that "even in the presence of abundant antigen . . . both memory and naïve T cells show an extended, and indistinguishable, delay in the onset of proliferation. Although memory cells can detect, and respond to, virus infection within a few hours, their proliferation did not begin until ~ 3 days after infection . . . ." Resp. Ex. M at 1.[44]

c. Respondent's Expert, Dr. Brent T. Harris

Dr. Harris obtained his medical degree from Georgetown University School of Medicine and doctorate in pharmacology from Georgetown University Graduate School. Tr. 99-100. He completed his internship and residency in pathology at Stanford University Medical School. Tr. 100. Dr. Harris subsequently did a two-year fellowship in the Neuropathology Section followed by postdoctoral fellowship for two years in the Department of Neurobiology. Resp. Ex. E at 1. His areas of expertise are anatomic pathology and neuropathology and neuroscience in general. Tr. 100. Dr. Harris is board certified in anatomic pathology and neuropathology. He is currently the Director of Neuropathology at Georgetown University Hospital and an Associate Professor in both neurology and pathology at Georgetown. Tr. 103. Dr. Harris also directs the brain bank and is the codirector of the histopathology and tissue shared resource. Id. He spends one-third of his time performing autopsies and examining specimens, and the remainder of his time teaching and doing biomedical research. Tr. 105.

Dr. Harris has performed approximately 1500 to 2000 autopsies, and in almost all of these, he has examined the heart. Tr. 105. During his anatomic pathology residency, he was trained to examine the heart and identify cardiac pathology. Tr. 106. He also saw many heart biopsies during his training at Stanford. Id.

1. Causation Theory

Dr. Harris opined that there is no evidence to support a causal relationship between the flu vaccine and lymphocytic myocarditis, and therefore, the vaccine did not play a role in Mr. Bolotaolo's death. Tr. 110. Although Dr. Harris has performed 1500 to 2000 autopsies, he explains that because lymphocytic myocarditis is a rare disease, he recalls making the diagnosis only four times, in two pediatric and two adult cases. Tr. 106. In both pediatric cases, the cause was enteroviruses. PCR analysis was not done in the adult cases, and therefore, no definitive cause was established. Id.

[43] Jeffrey Cohen et al., Kinetics of Serum Cytokines After Primary or Repeat Vaccination with the Smallpox Vaccine, 201 J. Infect. Diseases 1183 (2010).

[44] Jason Whitmire et al., Tentative T Cells: Memory Cells are Quick to Respond, but Slow to Divide, 4 PlosOne e1000041 (2008).

Lymphocytic myocarditis is defined by Dr. Harris as an "inflammation of the heart" characterized by "an influx of lymphocytes into the myocardium" with resulting heart damage. Tr. 114. After reviewing the autopsy performed by Dr. Patel and conducting an independent review of microscopic tissue slides and medical records, Dr. Harris opined that he agreed with Dr. Patel's findings and diagnosis of lymphocytic myocarditis. Dr. Harris explained that the major finding reported by Dr. Patel was "lymphocytic myocarditis affecting all areas of the heart . . . with multifocal areas of myocardial necrosis." Resp. Ex. D at 3. The "inflammation was [] primarily lymphocytic and T cell (CD3) in origin." Id. Dr. Harris reported that while not explicitly stated, Dr. Patel implies that the etiology could not be determined. Id. Dr. Harris noted that Dr. Patel did not attribute the cause to the flu vaccine. Tr. 118.

According to Dr. Harris, viral infection is the most common cause of lymphocytic myocarditis. Tr. 118. Although there are some reports of the influenza virus causing lymphocytic myocarditis, Dr. Harris is not aware of any medical literature associating the influenza vaccine with lymphocytic myocarditis. Tr. 123, 135-36. Dr. Harris agrees with Dr. Patel's enumerated list of potential causes, including viral, bacterial, autoimmune, collagen vascular diseases, drug/toxins, or idiopathic. Tr. 114; see Pet. Ex. 6 at 15 (autopsy report). Dr. Harris explained that most viruses that cause lymphocytic myocarditis require PCR testing to specifically identify the causal virus, since standard staining methodology does not reveal such viruses. Tr. 121. In this case, however, PCR testing was not done. Id.

The Dennert article cited by Dr. Harris summarizes the current state of medical knowledge about viral causes of lymphocytic myocarditis. Resp. Ex. F, Tab 2.[45] In Dennert, PCR analysis revealed a broad spectrum of viral infections responsible for myocarditis, with parvovirus (PVB19) and human herpes virus (HHV6) most frequently reported. Id. at 4. Other viruses found to cause lymphocytic myocarditis include enterovirus, adenovirus, Epstein Barr virus (EBV), and cytomegalovirus (CMV). Id. at 5. Consistent with the other experts, Dr. Harris testified that in viral induced lymphocytic myocarditis, it is both the viral infection and the body's immune response to the viral challenge that causes myocardial damage. Tr. 134.

Dr. Harris opined that the flu vaccine did not play a role in Mr. Bolotaolo's fatal lymphocytic myocarditis. Tr. 111. When Mr. Bolotaolo presented to the emergency department, he reported malaise and diarrhea, which Dr. Harris opined could have been caused by a virus. Id. Mr. Bolotaolo also had an elevated white blood cell count, which was "a sign of an infectious process." Tr. 112. On autopsy, heart tissue did not show evidence of fungus, bacteria, or parasites. Tr. 117. Viral inclusions were not seen, however, Dr. Harris explained that their absence does not rule out viral infected tissue. Tr. 117-18, 125. "[M]any viruses known to cause myocarditis [] do not show inclusions" using standard techniques and require more advanced diagnostic testing which was not done here.[46] Resp. Ex. D at 4; Resp. Ex. V at 1.

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[45] Robert Dennert et al., Acute Viral Myocarditis, 29 Eur. Heart J. 2073 (2008).

[46] At the conclusion of the hearing, the parties were asked to consult with their experts as to whether additional and more advanced testing could be performed. After consultation with their respective experts, the parties agreed that given the facts and circumstances in this case, further testing would not be helpful and was not warranted. See Status Rept. dated Aug. 1, 2018 (ECF No. 61).

In support of his opinion that viral inclusions may not be seen in cases of viral myocarditis, Dr. Harris cited an article by Cioc et al. In Cioc, PCR testing revealed the presence of viral infection of the myocardium in all 13 cases, including five cases of Coxsackievirus. However, "none of the 13 cases had evidence of viral inclusions." Resp. Ex. F, Tab 1 at 3.[47]

Dr. Harris also disagreed with Dr. Levin about the significance of the autopsy findings relative to the gastrointestinal tract. Tr. 125. Dr. Levin testified that he would have expected to see inflammation of the colon if Mr. Bolotaolo had a Coxsackie viral infection. Tr. 126. However, Dr. Harris explained that the colon tissue was autolyzed, or disintegrated, and thus, it was impossible to analyze the cellular components. Id. Living samples would have been necessary to obtain accurate results. Tr. 147.

Lastly, Dr. Levin testified that he was surprised that there was no lymphocytic reaction in any other organ. Dr. Harris responded that while "it could have gone either way[,]" viral myocarditis with selection specific to cardiac tissue is not unusual. Tr. 148.

In conclusion, Dr. Harris opined that viral or post-viral autoimmune myocarditis was the most likely etiology of Mr. Bolotaolo's myocarditis. Resp. Ex. D at 4. Because a "full viral infection workup was not performed . . . the cause is best designated as idiopathic." Id. at 5.

d. Respondent's Expert, Dr. Shane R. LaRue

Dr. LaRue obtained his medical degree at the Medical College of Wisconsin in Milwaukee. He completed three years of training in internal medicine, followed by one year of chief residency. Tr. 222. Following his internal medicine training, he did a three-year cardiology fellowship, followed by an additional fellowship in advanced heart failure and cardiac transplantation. Id. His specialty is advanced heart failure cardiology, and he cares for patients with heart failure, heart transplant patients, and patients who receive mechanical heart pumps and ventricular assist devices. Tr. 222-23. Dr. LaRue is board certified in internal medical, cardiovascular medicine, echocardiography, and advanced heart failure and cardiac transplantation. Tr. 223. Since 2014, Dr. LaRue has been an Assistant Professor of Medicine in the section of heart failure and cardiac transplantation at Washington University School of Medicine, St. Louis, where he spends eighty percent of his time caring for patients in a clinical setting. Tr. 226-27. The remaining twenty percent of his time is spent teaching and performing research. Tr. 227-28. He is involved in the diagnosis and treatment of patients with myocarditis. Tr. 227.

1. Causation Theory

Dr. LaRue opined that it was unlikely that the flu vaccine had anything to do with Mr. Bolotaolo's myocarditis or death. Tr. 232. It is not generally accepted in the cardiology medical community that a killed flu vaccine can cause lymphocytic myocarditis. Tr. 237, 250. And he

[47] Adina Cioc & Gerard Nuovo, Histologic and In Situ Viral Findings in the Myocardium in Cases of Sudden, Unexpected Death, 15 Mod. Pathol. 914 (2001).

stated that there are no case reports describing myocarditis associated with the flu vaccine.[48] Resp. Ex G at 3.

During the hearing, Dr. LaRue explained that he would expect there to be case reports or more VAERS reports of influenza vaccine associated myocarditis, if there was a causal association. Tr. 247-48. On cross-examination, he agreed that drug companies report rare events as a "one-in-a million reaction." Tr. 247. He also agreed that meta-analysis of several hundred thousand people would be unlikely to pick up a rare adverse reaction. Id. Dr. LaRue explained, however, that based on Centers for Disease Control (CDC) information,[49] one billion influenza vaccines are given approximately every eight years. Assuming a rare event of one-in-a-million, "this [myocarditis] would have happened ten times every eight years." Tr. 248. Dr. LaRue conceded that a rare adverse reaction could not be excluded. Id. But given his calculations, if myocarditis had occurred in association with the flu vaccine over the past few decades, he would expect there to be more VAERS reports. Id.

Dr. LaRue explained that Mr. Bolotaolo's clinical presentation was consistent with a viral etiology. Tr. 235. Mr. Bolotaolo had a fulminant presentation, became acutely ill, and suffered severe left ventricular dysfunction. Id. The onset was abrupt, with heart failure symptoms one evening and death the next day. Tr. 240. Also, Mr. Bolotaolo's "watery diarrhea raises concern that he had an acute enteroviral infection . . . which may have led to his development of myocarditis." Resp. Ex. G at 4.

While he agreed that cytokines are involved in the propagation of inflammation that lead to heart damage, Dr. Larue testified that he could not conceive how a vaccination could cause such extensive and severe myocarditis and was not aware of any evidence to support a causal relationship. Tr. 241-42, 255. He is not an immunologist and is not familiar with the mechanism of immune-mediated myocarditis. Tr. 258.

Citing the studies of myocarditis after smallpox vaccinations, Dr. LaRue stated that symptom onset was a median of 11 days post-vaccination, with a range of two to 42 days. Resp Ex. G at 4 (citing Resp. Ex. I, Tab 7 at 1);[50] see also Resp. Ex. T at 2. Dr. LaRue finds it "very unlikely that Mr. Bolotaolo developed vaccine related symptoms within one day of vaccination." Resp. Ex. G at 4 (citing medical record entry describing "body aches, chills, generalized weakness, and profuse, watery diarrhea since receiving the flu shot 3 days ago").

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[48] In his expert report, Dr. LaRue states: "There is currently no scientific evidence of a strong, clear relationship between [the] influenza vaccine and lymphocytic myocarditis." Resp. Ex. G at 3. This statement is not an accurate description of the petitioner's burden of proof. I do not rely upon nor am I persuaded by any reference to legal standards of causation espoused by any expert and the statement by Dr. LaRue does not inform my decision herein.

[49] Dr. LaRue filed data from the CDC regarding flu vaccination coverage in the United States for the 2014-15 influenza season as Resp. Ex. I, Tab 11.

[50] Juliette Morgan et al., Myocarditis, Pericarditis, and Dilated Cardiomyopathy After Smallpox Vaccination Among Civilians in the United States, January-October 2003, 46 Clin. Infect. Diseases S242 (2008).

VIII. Legal Framework

To receive compensation under the Program, the petitioner must prove either: (1) that Mr. Bolotaolo suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table—corresponding to a vaccine that she received, or (2) that he suffered an injury that was actually caused by a vaccination. See §§ 300aa-13(a)(1)(A) and 11(c)(1); Capizzano v. Sec'y of Health & Human Servs., 440 F.3d 1317, 1319-20 (Fed. Cir. 2006). Petitioner must show that the vaccine was "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface, 165 F.3d at 1352-53).

Because petitioner does not allege a Table injury, she must prove that the vaccine Mr. Bolotaolo received caused his death. To do so, she must establish, by preponderant evidence: (1) a medical theory causally connecting the vaccine and her injury ("Althen Prong One"); (2) a logical sequence of cause and effect showing that the vaccine was the reason for her injury ("Althen Prong Two"); and (3) a showing of a proximate temporal relationship between the vaccine and her injury ("Althen Prong Three"). § 300aa–13(a)(1); Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005).

Although petitioners need not identify the exact mechanism involved, their theory of causation must be informed by a "sound and reliable medical or scientific explanation." Knudsen v. Sec'y of Health & Human Servs., 35 F.3d 543, 548-49 (Fed. Cir. 1994); see also Veryzer v. Sec'y of Health & Human Servs., 98 Fed. Cl. 214, 223 (2011) (noting that special masters are bound by both § 300aa- 13(b)(1) and Vaccine Rule 8(b)(1) to consider only evidence that is both "relevant" and "reliable"), aff'd, 475 F. App'x 765 (Fed. Cir. 2012). If petitioners rely upon medical opinions to support their theory, the basis for the opinion and the reliability of that basis must be considered in the determination of how much weight to afford the offered opinion. See Broekelschen v. Sec'y of Health & Human Servs., 618 F.3d 1339, 1347 (Fed. Cir. 2010) ("The special master's decision often times is based on the credibility of the experts and the relative persuasiveness of their competing theories."); Perreira v. Sec'y of Health & Human Servs., 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) (stating that an "expert opinion is no better than the soundness of the reasons supporting it.") (citing Fehrs v. United States, 620 F.2d 255, 265 (Ct. Cl. 1980)).

Another important aspect of the causation-in-fact case law under the Vaccine Act concerns the factors that a special master may consider in evaluating the reliability of expert testimony and other scientific evidence relating to causation issues. In Daubert v. Merrell Dow Pharm., Inc., 509 U.S. 579 (1993), the United States Supreme Court listed certain factors that federal trial courts should utilize in evaluating proposed expert testimony concerning scientific issues. In Terran v. Sec'y of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999), the Federal Circuit ruled that it is appropriate for special masters to utilize Daubert's factors as a framework for evaluating the reliability of causation-in-fact theories actually presented in Program cases.

The Daubert factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." Terran, 195 F.3d at 1316, n.2 (citing Daubert, 509 U.S. at 592-95). In addition, where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their

competing theories." Broekelschen, 618 F.3d at 1347 (citing Lampe v. Sec'y of Health & Human Servs., 219 F.3d 1357, 1362 (Fed.Cir. 2000)). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." Snyder v. Sec'y of Health & Human Servs., 88 Fed. Cl. 706, 743 (quoting Gen. Elec. Co. v. Joiner, 522 U.S. 146 (1997)).

IX. Analysis

a. Althen Analysis

i. Althen Prong One: Petitioner's Medical Theory

Under Althen Prong One, petitioner must set forth a medical theory explaining how the vaccine at issue could have caused the alleged injury. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1375 (Fed. Cir. 2009); Pafford, 451 F.3d at 1355-56. Petitioners' theory of causation must be informed by a "sound and reliable medical or scientific explanation." Knudsen, 35 F.3d at 548; see also Veryzer, 98 Fed. Cl. at 223 (noting that special masters are bound by both § 300aa- 13(b)(1) and Vaccine Rule 8(b)(1) to consider only evidence that is both "relevant" and "reliable"). If petitioners rely upon a medical opinion to support their theory, the basis for the opinion and the reliability of that basis must be considered in the determination of how much weight to afford the offered opinion. See Broekelschen, 618 F.3d at 1347 (Fed. Cir. 2010) ("The special master's decision often times is based on the credibility of the experts and the relative persuasiveness of their competing theories."); Perreira, 33 F.3d at 1377 n.6 (stating that an "expert opinion is no better than the soundness of the reasons supporting it.") (citing Fehrs, 620 F.2d at 265)).

Petitioner has failed to set forth by preponderant evidence a sound and reliable medical theory explaining how the influenza vaccine could have caused Mr. Bolotaolo's lymphocytic myocarditis and death. The theory posited by Dr. Levin, as set forth in Ukimura and the other literature cited, relates to how the influenza viral infection can cause myocarditis, not the vaccine. Dr. Levin acknowledged the fact that the pathogenesis of influenza myocarditis is due in part to the "direct effect of the influenza virus infection." Pet. Ex. 10 at 4. Based upon the testimony of the experts, and medical literature, the mechanism whereby the influenza infection causes injury is two-fold, direct injury due to replication of viral proteins from the active virus and adaptive immune system response to [the] viral infection causing severe inflammation of the myocardium. However, petitioner did not provide evidence that the influenza vaccine, a killed flu vaccine, is able to cause direct injury to the myocardium. The literature cited by petitioner dealt with the smallpox vaccine, which contains a live virus, unlike the flu vaccine.

Fundamentally, Dr. Levin failed to acknowledge that the influenza vaccine and influenza viral infection evoke distinct immune responses. Dr. Levin used the terms "infection" and "vaccine reaction" and "virus" and "vaccine" synonymously without providing preponderant evidence to support his position. At the hearing, he agreed to provide medical literature in support of his opinion that the immune response to viruses and vaccines are identical. Subsequently, Dr. Levin submitted several articles, including Amoah and Song, however, they do not address the similarity of infections and vaccines.

In Amoah, the authors note that inflammatory monocytes, neutrophils, macrophages, and CD4+ cells are important in innate and adaptive immune responses that contribute to autoimmune myocarditis. However, these cells were not reported in Mr. Bolotaolo's autopsy. Amoah does reference T cell lymphocytic proliferation found along with macrophage antigens from giant cells. But the autopsy report here specifically states that giant cells were not seen. And in Song, the authors studied the dysregulation of CD4+ cells, however, CD4+ cells were not reported in Mr. Bolotaolo's autopsy.

Moreover, the scientific study by Engler done on the smallpox and influenza vaccines does not support Dr. Levin's theory that the flu vaccine causes cytokine release which injures myocardium. In Engler, cytokine elevation occurred only in the smallpox vaccine recipients and not the influenza vaccinees. Petitioner provided no evidence to show that the mechanism by which a live virus smallpox vaccine causes myocarditis applies to the influenza vaccine.

Dr. Levin's testimony was difficult to follow and at times inconsistent. In his first expert report, Dr. Levin testified that the adaptive immune system was at play, however, at the hearing, he testified that the most likely causative system was the innate immune system, and the cytokines released in response to the flu vaccine. And at the hearing, however, Dr. Levin emphasized that the myocardial damage was done primarily by the innate immune system. His opinions were less persuasive due to this inconsistent testimony.[51]

Also, Dr. Levin's reliance on the Feeley and Ukimura articles cited in support of his theory is misplaced. Feeley describes the "autoimmune cytotoxic T cell response" which Dr. Levin embraced as his theory. Tr. 81-82. In Feeley, however, the mechanism of "autoimmune cytotoxic T cell response" was used to explain the pathogenesis of the "chronic/persistent phase" of myocarditis. However, Mr. Bolotaolo had acute fulminant lymphocytic myocarditis. A theory that relates to chronic myocardial injury is not consistent with the injury alleged by petitioner.

In her post-hearing memorandum, petitioner cites two vaccine program cases involving myocarditis that have resulted in settlements.[52] While Dr. Levin did not opine about these cases, a review of the decisions reveal factual differences which distinguish them from this case. In Bond, the petitioner suffered "hypersensitivity myocarditis." Dr. Levin explained that hypersensitivity myocarditis involves B cells, and the relevant histology is eosinophils, not lymphocytes. The second case, Gomez, involved the HPV vaccine,[53] which is not similar to the influenza vaccine. Death occurred the day after vaccination and the histology is not identified. The facts and

[51] In his post-hearing submission, respondent provided a list of cases in which Dr. Levin's expert opinion has been excluded by a court or criticized by another special master. Resp. Posthr'g Submissions at 6 n.19. While I have reviewed the information provided, I do not base my decision in this case on what may have occurred in any other legal proceeding or case.

[52] See Gomez v. Sec'y of Health & Human Servs., No. 15-160V, 2016 WL 6072391 (Fed. Cl. Spec. Mstr. Sept. 21, 2016); Bond v. Sec'y of Health & Human Servs., No. 08-713V, 2010 WL 1732266 (Fed. Cl. Spec. Mstr. Jan. 20, 2010).

[53] The HPV (Human Papillomavirus) vaccine is not manufactured from a live, attenuated or inactivated, killed virus, but uses virus-like particles derived from proteins specific to papillomavirus.

circumstance of both cases are so different that it is difficult to postulate as to how they might support Dr. Levin's theory here.

There are similarities with the theory proposed here by petitioner with the theory posited by petitioner in the Boatman case. See Boatman v. Sec'y of Health & Human Servs., 941 F.3d 1351 (Fed. Cir. 2019). In Boatman, the petitioner's expert, Dr. Miller, opined that the "upregulation of cytokines" following vaccination was similar to the "upregulation of cytokines associated with a mild infection." Id. at 1356. The Federal Circuit did not find preponderant evidence that petitioner had presented a "sound and reliable" medical theory that vaccines were like infections so as to implicate the Triple Risk Model of causation applicable to SIDS. My finding here is consistent with the Federal Circuit's finding in Boatman.

Upon review of all of the evidence, I find that it does not support the mechanistic theory proposed by Dr. Levin. A special master does not need to credit "expert opinion testimony that is connected to the existing data or methodology 'only by the ipse dixit of the expert.'" Jarvis v. Sec'y of Health & Human Servs., 99 Fed. Cl. 47, 61 (2011) (quoting Cedillo v. Sec'y of Health & Human Servs., 617 F.3d 1328, 1339 (Fed. Cir. 2010)).

ii. Althen Prong Two: Logical Sequence of Cause and Effect

Under Althen Prong Two, petitioners must prove by a preponderance of the evidence that there is a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." Capizzano, 440 F.3d at 1324 (quoting Althen, 418 F.3d at 1278). "Petitioner[s] must show that the vaccine was the 'but for' cause of the harm . . . or in other words, that the vaccine was the 'reason for the injury.'" Pafford, 451 F.3d at 1356 (citations omitted). Because petitioner failed to present a sound or reliable theory as to how the influenza vaccine can cause lymphocytic myocarditis, she has also failed to show a logical sequence of cause and effect as to how the influenza vaccine caused Mr. Bolotaolo's lymphocytic myocarditis and death.

As described above, the petitioner failed to show that the histology in this case is consistent with vaccine associated myocarditis. The pathologist who performed Mr. Bolotaolo's autopsy made a finding of lymphocytic myocarditis. All of the experts agree that Mr. Bolotaolo had lymphocytic myocarditis. Lymphocytic myocarditis has been reported after viral infection, but there is no evidence submitted by the petitioner to establish that it has been reported in cases of vaccine associated myocarditis. The evidence filed in this case states that the histology associated with smallpox vaccination is eosinophilic myocarditis. Resp. Ex. A at 3; Resp. Ex. C, Tab 6 at 6.

Moreover, by virtue of his experience conducting autopsies and reviewing myocardial tissue, and because he cited relevant literature in support of his opinions, Dr. Harris' opinions as to the findings on autopsy and cause of death were more persuasive than those of Dr. Levin. For example, Dr. Harris explained that inclusions are not seen for many viruses that cause myocarditis using standard techniques. More advanced diagnostic testing is required which was not done here. The Cioc article Dr. Harris filed in support of this opinion was relevant and showed that in 13 cases where PCR testing revealed the presence of viral infection, viral inclusions were not seen.

Further, there were times when Dr. Levin's testimony was somewhat exaggerated, which decreased his credibility. He testified that Mr. Bolotaolo's increased white blood cell count was "absolute and unequivocal proof that there was an elevation" in cytokines which would be expected

after vaccination. See Tr. 272-73. However, an elevated white blood cell count is not a specific finding, and it is not "absolute and unequivocal proof" that cytokine increase is caused by vaccination as Dr. Levin suggested. And on cross-examination, Dr. Levin conceded that an elevated count is consistent with a viral infection. See Tr. 282. In contrast, Dr. Harris did not overstate the facts or findings, or implications based on the evidence, and thus, he was more credible and persuasive.

iii. Althen Prong Three: Proximate Temporal Relationship

Under Althen Prong Three, petitioners must provide "preponderant proof that the onset of symptoms occurred within a timeframe for which, given the understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." De Bazan v. Sec'y of Health & Human Servs., 539 F.3d 1347, 1352 (Fed. Cir. 2008). The acceptable temporal association will vary according to the particular medical theory advanced in the case. See Pafford, 451 F.3d at 1358. A temporal relationship between a vaccine and an injury, standing alone, does not constitute preponderant evidence of vaccine causation. See, e.g., Veryzer v. Sec'y of Health & Human Servs., 100 Fed. Cl. 344, 356 (2011) (explaining that "a temporal relationship alone will not demonstrate the requisite causal link and that petitioner must posit a medical theory causally connecting the vaccine and injury").

Here there is a temporal relationship between Mr. Bolotaolo's vaccination and his death. However, a temporal relationship alone cannot establish causation, nor is it sufficient on its own to meet Althen Prong Three. Veryzer, 100 Fed. Cl. at 356. Rather, there must be "preponderant proof that the onset of symptoms occurred within a timeframe for which, given the understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." De Bazan, 539 F.3d at 1352. Under Althen Prong Three, the petitioner must establish the timeframe for which it is medically acceptable to infer causation, assuming Mr. Bolotaolo's death was caused by the vaccination, and they must show that his death occurred in that timeframe. See Shapiro v. Sec'y of Health & Human Servs., 105 Fed. Cl. 353 (Fed. Cl. 2012).

Dr. Levin testified that the temporal association of vaccination and myocarditis/death three days post-vaccination was reasonable given his mechanism of a primary innate immune response causing inflammation triggered by cytokines and T lymphocytes. He cited several sources in support of his opinion. The manufacturer's package insert states that systemic adverse reactions can occur within three days, and the Song study reported that severe inflammation of the heart was seen in that same timeframe. The Bracamonte-Baran article reported longer onset periods, ranging from seven to 21 days.

Dr. Whitton disagreed that the level of inflammation seen on autopsy here could occur within three days of vaccination. He relied on his own animal studies, as well as studies reported in the literature, showing that lymphocytic myocarditis was not seen in heart tissue until six days after viral infection. Dr. Whitton also cited the Engler paper, which established that inflammation after the smallpox vaccine occurred from four to 27 days, with a peak of eight to nine days. However, Morgan, another smallpox study paper, reported a symptom onset range of two to 42 days post vaccination.

Given the symptom onset reported in Morgan of two days, and since the vaccine package insert identifies onset of within three days for systemic reactions, there is some evidence to support

Dr. Levin's opinion as to temporal association. Therefore, I find that petitioner has provided preponderant evidence of a temporal association. However, petitioner failed to provide preponderant evidence of a reliable medical theory and a logical sequence of cause and effect under Althen Prongs One and Two, respectively. A temporal relationship alone is not sufficient to establish causation in fact without preponderant evidence of the two remaining factors. See Veryzer, 98 Fed. Cl. at 227 (citing Grant, 956 F.2d at 1148). Thus, petitioner's failure to meet Althen Prongs One and Two means that she cannot be compensated. See, e.g., Koehn v. Sec'y of Health & Human Servs., 2013 WL 3214877, at *29 (Fed. Cl. Spec. Mstr. May 30, 2013) (citing Hibbard v. Sec'y of Health & Human Servs., 698 F.3d 1355, 1364-65 (Fed. Cir. 2012) (holding the special master did not err in resolving the case pursuant to Prong Two when respondent conceded that petitioner met Prong Three)), aff'd, 773 F.3d 1239 (Fed. Cir. 2014).

b. Alternative Causation

Because petitioner did not meet her burden of proof on causation, respondent does not have the burden of establishing that a factor unrelated to the vaccination caused Mr. Bolotaolo's death. See Doe v. Sec'y of Health & Human Servs., 601 F.3d 1349, 1358 (Fed. Cir. 2010) ("[petitioner] Doe never established a prima facie case, so the burden (and attendant restrictions on what 'factors unrelated' the government could argue) never shifted"). Further, although respondent's experts identified an alternative cause of viral infection, and Dr. Harris opined that viral or post-viral autoimmune myocarditis was the most likely cause of Mr. Bolotaolo's myocarditis, because a full viral infection workup was not performed, the cause is best defined as idiopathic. Thus, it is not known what caused Mr. Bolotaolo's myocarditis and death.

X. Conclusion

The petitioner has suffered as a result of her father's illness and death, and I extend my deepest sympathy to her and her family for the loss of Mr. Bolotaolo. However, I cannot decide this case based upon my sympathy for petitioner but must decide it on my analysis of the evidence.

For all of the reasons discussed above, I find that the petitioner has not established entitlement to compensation and her petition must be dismissed. In the absence of a timely filed motion for review pursuant to Vaccine Rule 23, the Clerk of the Court **SHALL ENTER JUDGMENT** in accordance with this Decision.

IT IS SO ORDERED.

s/Nora Beth Dorsey
Nora Beth Dorsey
Special Master

VAERS Event Details

Details for VAERS ID: 249021-1

Event Information			
Patient Age	1.08	**Sex**	Male
State / Territory	New Jersey	**Date Report Completed**	
Date Vaccinated	2005-11-03	**Date Report Received**	2005-12-09
Date of Onset	2005-11-10	**Date Died**	2005-11-10
Days to onset	7	**Grantee**	Non-Grantee
Vaccine Administered By	Public	**Vaccine Purchased By**	Public **
Mfr/Imm Project Number	NONE	**Report Form Version**	1
Recovered	No	**Serious**	Yes

* VAERS 2.0 Report Form Only
** VAERS-1 Report Form Only
"Not Applicable" will appear when information is not available on this report form version.

Event Categories	
Death	Yes
Life Threatening	No
Permanent Disability	No
Congenital Anomaly / Birth Defect *	N/A
Hospitalized	No
Days in Hospital	None
Existing Hospitalization Prolonged	No
Emergency Room / Office Visit **	No
Emergency Room *	N/A
Office Visit *	N/A

* VAERS 2.0 Report Form Only
** VAERS-1 Report Form Only
"N/A" will appear when information is not available on this report form version.

Vaccine Type	Vaccine	Manufacturer	Lot	Dose	Route	Site
HAEMOPHILUS B CONJUGATE VACCINE	HIB (PEDVAXHIB)	MERCK & CO. INC.	0347R	UNK	IM	LA
INFLUENZA VIRUS VACCINE, TRIVALENT (INJECTED)	INFLUENZA (SEASONAL) (FLUZONE)	SANOFI PASTEUR	U1904AA	UNK	IM	RL
PNEUMOCOCCAL, 7-VALENT VACCINE (PREVNAR)	PNEUMO (PREVNAR)	PFIZER\WYETH	A25962H	UNK	IM	RA

Symptom
CARDIAC FAILURE
IRRITABILITY
MYOCARDITIS

Adverse Event Description
Received vaccine 11/03/2005, admitted in heart failure, myocarditis 11/10/2005, Died 11/10/2005. Increasingly cranky for 2 days procedding admission to hospital.

Lab Data	Current Illness	Adverse Events After Prior Vaccinations
	History of RAD	

Medications At Time Of Vaccination	History/Allergies
Pulmicort, Zantac, Singulair, Albuterol, AccuNeb	Premie, asthma,

Note: Submitting a report to VAERS does not mean that healthcare personnel or the vaccine caused or contributed to the adverse event (possible side effect).

Notes:

Caveats: Data contains VAERS reports processed as of 9/14/2019. The VAERS data in WONDER are updated monthly, yet the VAERS system receives continuous updates including revisions and new reports for preceding time periods. More information.

Help: See The Vaccine Adverse Event Reporting System (VAERS) Documentation for more information.

Query Date: Nov 6, 2019 2:47:30 PM

Suggested Citation:

United States Department of Health and Human Services (DHHS), Public Health Service (PHS), Centers for Disease Control (CDC) / Food and Drug Administration (FDA), Vaccine Adverse Event Reporting System (VAERS) 1990 - last month, CDC WONDER On-line Database. Accessed at http://wonder.cdc.gov/vaers.html on Nov 6, 2019 2:47:30 PM

VAERS Event Details

Details for VAERS ID: 393060-1

Event Information			
Patient Age	42.00	**Sex**	Male
State / Territory	Unknown	**Date Report Completed**	2010-07-10
Date Vaccinated	2009-11-17	**Date Report Received**	2010-07-19
Date of Onset	2010-02-09	**Date Died**	2010-02-09
Days to onset	84	**Grantee**	Non-Grantee
Vaccine Administered By	Military	**Vaccine Purchased By**	Military **
Mfr/Imm Project Number	NONE	**Report Form Version**	1
Recovered	No	**Serious**	Yes

* VAERS 2.0 Report Form Only
** VAERS-1 Report Form Only
"Not Applicable" will appear when information is not available on this report form version.

Event Categories	
Death	Yes
Life Threatening	No
Permanent Disability	No
Congenital Anomaly / Birth Defect *	N/A
Hospitalized	No
Days in Hospital	None
Existing Hospitalization Prolonged	No
Emergency Room / Office Visit **	No
Emergency Room *	N/A
Office Visit *	N/A

* VAERS 2.0 Report Form Only
** VAERS-1 Report Form Only
"N/A" will appear when information is not available on this report form version.

Vaccine Type	Vaccine	Manufacturer	Lot	Dose	Route	Site
INFLUENZA (H1N1) MONOVALENT (INJECTED)	INFLUENZA (H1N1) (H1N1 (MONOVALENT) (NOVARTIS))	NOVARTIS VACCINES AND DIAGNOSTICS	102126P1A	1	IM	LA

Symptom
AUTOPSY
DEATH
MYOCARDITIS

Adverse Event Description
Pt died. Autopsy revealed Giant cell myocarditis. Pt received H1N1 vaccine 2 1/2 months prior. Unsure if related.

Lab Data	Current Illness	Adverse Events After Prior Vaccinations
Autopsy as above	None	

Medications At Time Of Vaccination	History/Allergies
Trazodone; TOPAMAX; PRILOSEC; ZOMIG PRN; dicyclomine; KLONOPIN	sleep apnea; migraines; obesity; insomnia; allergic rhinitis; ED; TOB use,

Note: Submitting a report to VAERS does not mean that healthcare personnel or the vaccine caused or contributed to the adverse event (possible side effect).

Notes:

Caveats: Data contains VAERS reports processed as of 9/14/2019. The VAERS data in WONDER are updated monthly, yet the VAERS system receives continuous updates including revisions and new reports for preceding time periods. More information.

Help: See The Vaccine Adverse Event Reporting System (VAERS) Documentation for more information.

Query Date: Nov 6, 2019 2:49:43 PM

Suggested Citation:

United States Department of Health and Human Services (DHHS), Public Health Service (PHS), Centers for Disease Control (CDC) / Food and Drug Administration (FDA), Vaccine Adverse Event Reporting System (VAERS) 1990 - last month, CDC WONDER On-line Database. Accessed at http://wonder.cdc.gov/vaers.html on Nov 6, 2019 2:49:43 PM